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(54) **Skin treatment compositions containing biotin antagonists**

(57) A cosmetically acceptable composition for topical application to human skin or hair in order to reduce greasiness comprises, at a concentration of from 0.0001M to 0.5M, a biotin antagonist which is capable of blocking the activity of the biotin dependent enzyme acetyl-SCoA-carboxylase implicated in sebum production; together with a carrier other than water as an aid to delivering the biotin antagonist to the sebaceous gland.

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SPECIFICATION

Skin treatment composition

The invention relates to cosmetic compositions for topical application to the skin or hair, particularly to compositions that are effective in reducing the amount of sebum which normally accumulates on the skin surface.

Normal healthy human skin secretes a natural lubricant known as sebum, which usually serves to keep the skin surface soft, pliable, conditioned and, to some extent, protected.

Sebum, a complex mixture of lipid substances, is secreted from sebaceous glands associated with hair follicles over most of the body surface, in particular the scalp, face, upper chest and shoulders.

Normal healthy human skin also secretes sweat from eccrine and apocrine glands. Eccrine sweat is associated with both the control of body temperature and the secretion of waste products: it consists mainly of water but contains also inorganic and organic components, notably sodium chloride and lactic acid. Apocrine sweat is associated with adrenergic stimulus and in addition to water and sodium chloride, also contains odour producing proteins, lipoproteins and lipids.

Whereas the secretion at the skin surface of sebum and sweat represents a normal and necessary bodily function, excessive production of these secretions can result in a film on the skin surface which is oily or greasy in nature and which can be disliked to the extent that the human subject will go to considerable trouble to remove it, for example by tissue wiping, by excessive washing or by application of make-up, so as to block skin pores from which sebum and sweat are released onto the skin surface.

The control of lipids secreted onto the skin, to provide a proper balance whereby the skin remains supple and protected yet without being excessively greasy, has accordingly presented a problem to the cosmetician, and hitherto it has been difficult in a non-clinical environment to strike the proper balance by the simple application of a topical product. In any case, efforts in this direction have concentrated solely on the removal of excess sebum after secretion onto the skin surface.

It has, however, now been discovered that, by topical application to skin or hair of one or more special biotin antagonists dissolved in a suitable liquid carrier, the synthesis of sebum in the sebaceous glands can be suppressed so that a reduced amount of sebum is secreted onto the skin surface.

It has been proposed by Gunther in US—A—4 243 655 to employ very low concentrations of biotin antagonists in products such as toothpastes and mouthwashes for oral use. Gunther observed that many of the microorganisms implicated in the production of dental caries require an outside source of biotin, usually present in saliva, and hence by blocking biotin uptake by application of a large excess of a biotin antagonist, conditions are made unfavourable for plaque and acid formation by the oral microflora. The concentrations of biotin antagonists avocated by Gunther were 0.00056% by weight for toothpastes, and 0.00004% by weight for mouthwashes, and 0.0011% for toothpowder.

We have shown that topically applied compositions containing as little as 0.002% by weight of biotin antagonist are insufficient to influence sebum production and that a higher concentration of these materials is accordingly required before any significant reduction in sebum production is observed.

By "biotin antagonist" is meant any compound which can inhibit the biological function of biotin.

While studying the effect of biotin antagonists on sebum secretion, it was discovered that most of the biotin occurring naturally in skin is located in the sebaceous glands. It has also been noted that a biotin dependent enzyme, acetyl-SCoA-carboxylase, involved in lipid synthesis is located in the sebaceous gland, and that its activity can be impaired by the introduction of biotin antagonists. Hence the synthesis of lipids in the sebaceous glands is reduced and consequently the skin surfaces where sebaceous glands are found are less greasy.

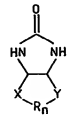
The role of biotin in the function of acetyl-SCoA-carboxylase, the inactivation of this enzyme with biotin antagonists and evidence to support the interference by biotin antagonists of skin lipid synthesis will be outlined later in this specification.

The invention is accordingly concerned with the topical application of biotin antagonist at a concentration sufficient to block the activity of biotin dependent enzymes located in the sebaceous gland which are implicated in lipid synthesis.

More particularly, the invention provides a cosmetically acceptable composition for topical application to human skin or hair which comprises, at a concentration of from 0.0001M to 0.5M, a biotin antagonist or a salt thereof, which is cable of blocking the activity of the biotin dependent enzyme acetyl-SCoA-carboxylase; together with carrier other than water.

Any cosmetically acceptable biotin antagonist can be employed in the composition to block the activity of acetyl-SCoA-carboxylase and so reduce sebaceous lipid synthesis.

A preferred class of biotin antagonists is that having the structure (I):

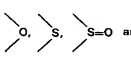


(I)

where n is zero or 1

and when n is zero, X is —CH_2, and Y is —$(CH_2)_mZ$,

and when n is 1,

R is chosen from  and 

X is  , and Y is 

where

m is an integer of from 1 to 8, and

Z is chosen from —CH_2COOH, —CH=CHCOOH, —$CH(CH_3)COOH$, —CH_2COOCH_3, —$NHNH_2$ and —SO_3H

provided that when R is

and Z is —CH_2COOH,

then m is an integer of from 1 to 3 or 5 to 8.

Examples of biotin antagonists having the structure (I) where n is zero and where Z is —CH_2COOH are:

trisnordesthiobiotin,	where m is 1
bisnordesthiobiotin,	where m is 2
nordesthiobiotin,	where m is 3
desthiobiotin,	where m is 4
homodesthiobiotin,	where m is 5
bishomodesthiobiotin,	where m is 6
trishomodesthiobiotin,	where m is 7
and	
tetrahomodesthiobiotin,	where m is 8

Further examples of biotin antagonists having the structure (I) where n is 1 and where R is

and where Z is —CH_2COOH are:

trisnorbiotin sulphoxide,	where m is 1
bisnorbiotin sulphoxide,	where m is 2
norbiotin sulphoxide,	where m is 3
biotin sulphoxide,	where m is 4
homobiotin sulphoxide,	where m is 5
bishomobiotin sulphoxide,	where m is 6

and trishomobiotin sulphoxide, where m is 7

Further examples of biotin antagonists having the structure (I) where n is 1 and where R is

and where Z is —CH_2COOH are:

trisnorbiotin sulphone,	where m is 1
bisnorbiotin sulphone,	where m is 2
norbiotin sulphone,	where m is 3
biotin sulphone,	where m is 4
homobiotin sulphone,	where m is 5
bishomobiotin sulphone, and	where m is 6
trishomobiotin sulphone,	where m is 7.

Further examples of biotin antagonists having the structure (I) where n is 1 and where R is 

and where Z is —CH_2COOH are:

trisnorbiotin,	where m is 1
bisnorbiotin,	where m is 2
norbiotin,	where m is 3
homobiotin,	where m is 5
bishomobiotin, and	where m is 6
trishomobiotin,	where m is 7

A further exemple of biotin antagonists having the structure (I) where n is 1 and where R is 

and where Z is —CH=CHCOOH is:

α-dehydrobiotin,	where m is 3

A further example of biotin entegonist having the structure (I) where n is 1 and where R is 

and where Z is —$CH(CH_3)COOH$ is:

α-methyl biotin,	where m is 4

Further examples of biotin antagonists having the structure (I) where n is 1, and where R is

and where Z is —CH_2COOH are:

trisnoroxybiotin,	where m is 1
bisnoroxybiotin,	where m is 2
noroxybiotin,	where m is 3
oxybiotin,	where m is 4
homooxybiotin,	where m is 5
bishomooxybiotin, and	where m is 6
trishomooxybiotin,	where m is 7

Further examples of biotin antagonists having the structure (I) where n is 1 and where R is 

and where Z is —SO_3H are:

trisnoroxybiotin sulphonic acid,	where m is 2
bisnoroxybiotin sulphonic acid,	where m is 3
noroxybiotin sulphonic acid,	where m is 4
oxybiotin sulphonic acid,	where m is 5
homooxybiotin sulphonic acid,	where m is 6
bishomooxybiotin sulphonic acid,	where m is 7
trishomooxybiotin sulphonic acid,	where m is 8

Further examples of biotin antagonists having the structure (I) and where n is 1 and R is

and where Z is —CH_2COOCH_3 are:

trisnorbiotin methyl ester,	where m is 1
bisnorbiotin methyl ester,	where m is 2
norbiotin methyl ester,	where m is 3
biotin methyl ester,	where m is 4
homobiotin methyl ester,	where m is 5
bishomobiotin methyl ester,	where m is 6
trishomobiotin methyl ester,	where m is 7
tetrahomobiotin methyl ester,	where m is 8

Further examples of biotin antagonists having the structure (I) and where n is 1 and R is

and where Z is —CH_2COOCH_3 are:

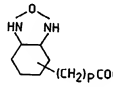
trisnorbiotin sulphone methyl ester,	where m is 1
bisnorbiotin sulphone methyl ester,	where m is 2
norbiotin sulphone methyl ester,	where m is 3
biotin sulphone methyl ester,	where m is 4
homobiotin sulphone methyl ester,	where m is 5
bishomobiotin sulphone methyl ester,	where m is 6
trishomobiotin sulphone methyl ester,	where m is 7
tetrahomobiotin sulphone methyl ester,	where m is 8

Further examples of biotin antagonists heving the structure (I) where n is 1 and where R is

and where Z is —$NHNH_2$ are:

trisnorbiotin hydrazide,	where m is 2
bisnorbiotin hydrazide,	where m is 3
norbiotin hydrazide,	where m is 4
biotin hydrezide,	where m is 5
homobiotin hydrazide,	where m is 6
bishomobiotin hydrazide,	where m is 7
trishomobiotin hydrazide,	where m is 8

A further class of biotin antagonists is that having the structure (II):



(II)

where p is 2 to 5

Specific examples of biotin antagonists having the structure (II) are:

γ-(2,3-ureylenecyclohexyl)butyric acid,	where p is 3
δ-(2,3-ureylenecyclohexyl)valeric acid,	where p is 4
γ-(3,4-ureylenecyclohexyl)butyric acid, and	where p is 3
δ-(3,4-ureylenecyclohexyl)valeric acid,	where p is 4

Examples of other biotin antagonists ere:

2-oxo-4-Imidazolidine caproic acid, thiazolidine,
methyl-1,3-acetyl-4-thiazolidine carboxylate, 1,2-propyl-2-acetyl-4-thiazolidine carboxylate
methyl ester and its hydrezide,
2-piperidone-6-carboxylic acid hydrazide,
γ-(2-carboxy-3-indolyl)butyric acid hydrazide,
2-Imidazoline-4-carboxylic acid hydrazide,
2-imidazoline-4-caproic acid hydrazide,
2-Imidazoline-4-valeric acid hydrazide,
ureylenetetrahydrofuryl aliphatic sulphonic acids, benzyl thioethers,
semicarbazides of biotin, and
bishydrazides of suberic and sebacic acids.

It is to be understood that the above examples of biotin antagonists include all possible stereoisomers as appropriate.

The most preferred biotin antagonists for use in compositions according to the invention are:

biotin sulphone
biotin sulphone methyl ester
α-dehydrobiotin
biotin hydrazide
homobiotin
homobiotin methyl ester

A biotin antagonist can be used alone in the composition or in admixture with one or more other biotin antagonists and/or biotin antagonist salts.

The biotin antagonists should be present in the composition in an amount which will effectively decrease the activity of the enzyme acetyl-SCoA-carboxylase and hence reduce the lipid synthesis in the sebaceous glands so that less sebum is produced. The composition should accordingly comprise a biotin antagonist at a concentration of from 0.0001M to 0.5M, preferably from 0.001M to 0.1M and most preferably from 0.01M to 0.1M.

It is apparent that if the composition contains the biotin antagonist at a concentration of less than 0.0001M, then the secretion of sebum at the skin surface is unlikely to be reduced, whereas if the ccomposition contains the biotin antagonist at a concentration of more than 0.5M, then it is unlikely that any extra benefit in terms of reduction of sebum secretion at the skin surface will be apparent compared with that obtained using a composition in which the biotin antagonist is present at a concentration of 0.5M.

Expressed in terms of weight percentage, the biotin antagonist should form from about 0.004% to about 10%, preferably 0.03% to 2%, most preferably 0.2% to 2% by weight of the composition.

The composition should also comprise a carrier other than water to enable the biotin antagonist to be conveyed to the sebaceous gland.

The selection of a carrier for biotin antagonists in compositions of the invention presents a wide range of possibilities depending on the required product form of the composition. Suiteble carriers can be classified as described hereinafter.

It should be explained that carriers are substances which can act as diluents, dispersants, or vehicles, as well as solvents for biotin antagonists, and which therefore ensure that they can be applied to and distributed evenly over the skin at an appropriate concentration; the carrier is preferably one which can aid penetration of the biotin antagonist into the sebeceous glands, thus ensuring that the effectiveness of the applied biotin antagonists is prolonged because of improved substantivity. Compositions according to this invention can include water, which can act as a carrier, provided that there is also present at least one cosmetically acceptable cerrier other than water.

Carriers other than water that can be used in compositions according to the invention can include solids or liquids such as emollients, propellants, solvents, humectants, thickeners and powders. Examples of each of these types of carriers, which can be used singly or as mixtures of one or more carriers, are as follows:

Emollients, such as stearyl alcohol, glyceryl monoricinoleate, glyceryl monostearate, propane-1,2-diol, butane-1,3-diol, mink oil, cetyl alcohol, isopropyl isostearate, stearic acid, isobutyl palmitate, isocetyl stearate, oleyl alcohol, isopropyl laurate, hexyl laurate, decyl oleate, octadecan-2-ol, isocetyl alcohol, cetyl palmitate, dimethylpolysiloxane, di-n-butyl sebacate, isopropyl myristate, isopropyl palmitate, isopropyl stearate, butyl stearate, polyethylene glycol, triethylene glycol, lanolin, castor oil, acetylated lanolin alcohols, petroletum, mineral oil, butyl myristate, isostearic acid, palmitic acid, isopropyl linoleate, lauryl lactate, myristyl lactete, decyl oleate, myristyl myristete;

Propellants, such as trichlorofluoromethane, dichlorodifluoromethane, dichlorotetrafluoroethane, monochlorodifluoromethane, trichlorotrifluoroethane, propane, butane, isobutene, dimethyl ether, carbon dioxide, nitrous oxide;

Solvents, such as ethyl alcohol, methylene chloride, isopropanol, castor oil, ethylene glycol monoethyl ether, diethylene glycol monobutyl ether, diethylene glycol monoethyl ether;

Humectants, such as glycerin, sorbitol, sodium 2-pyrrolidone-5-carboxylate, soluble collagen, dibutyl phthalate, gelatin;

Powders, such as chalk, talc, fullers eerth, kaolin, starch, gums, colloidal silicon dioxide, sodium polyacrylate, tetra alkyl and/or trialkyl aryl ammonium smectites, chemicelly modified magnesium aluminium silicate, organically modified montmorillonite cley, hydrated aluminium silicate, fumed silica, carboxyvinyl polymer, sodium carboxymethyl cellulose, ethylene glycol monostearate.

The preferred carrier is e lower alkenol, preferebly e C_1 to C_4 alkanol.

The most preferred C_1 to C_4 elkenol is ethanol or isopropanol or e mixture thereof.

The amount of carrier in the composition, including weter if present, should preferably be sufficient to carry et least a portion of the biotin antagonist to the sebaceous gland which is sufficient effectively to reduce sebum secretion onto the skin surface. The amount of liquid carrier can comprise the major portion of the composition, particularly where little or no other ingredients are present in the composition.

The composition will accordingly comprise from 50 to 99.996% and preferably from 90 to 99.5% by weight of the carrier or carriers.

The compositions according to the invention can contain ingredients other than those already mentioned, dapending on tha form of tha intended product. It is, for example, possible to include antiseptics, preservatives, antioxidants, emulsifiers, perfumes, colouring agents and detergents.

The composition according to tha invention can also be employed as a vehicle for a wida variety of cosmatically or pharmaceutically active ingredients, particularly ingredients which have some beneficial effect when applied to the skin or hair.

The composition thus provides a means whereby such active ingredients can be diluted, dispersed, conveyed to and distributed on tha skin surface or on the hair at an appropriate concentration.

Especially preferred examples of active ingredients include moisturisers, anti-acne agants, sunscreen agents, garmicidas, daodorants, antiperspirants, healing agents and datargents.

The invention also provides a process for the preparation of a cosmetic composition for topical application to skin or hair which comprises mixing a biotin antagonist with a suitabla carrier to provida a concentration of from 0.0001M to 0.5M.

The compositions of the invention can ba formulated as liquids, for axample as a lotion or milk for usa in conjunction with an applicator such as a roll-ball applicator, or a spray davice such as an aarosol can containing propallant, or a containar fitted with a pump to dispense the liquid product.

Alternatively, the compositions of tha invantion can be solid or semi-solid, for example creams or gals, for use in conjunction with a suitabla applicator or simply a tube, bottle or lidded jar.

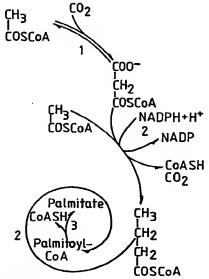
The invention accordingly also provides a closed containar containing a cosmetic composition as harain defined.

Compositions of the invention are intended especially for topical application to human skin or hair, in particular when the skin surface or the hair has become excassivaly greasy due to an accumulation of sebum.

Topical application of the composition will accordingly reduce tha superficial "grease" without unduly dafatting the skin. The skin or hair will then remain in a healthy, non-greasy condition, usually for saveral hours. It can also usafully be employed in the treatment of acne as excess sabum production is a universal accompaniment of acne.

An explanation of the role of biotin in the function of acetyl-SCoA-carboxylase and the inactivation of this enzyme with biotin antagonists

Biotin is an assantial cofactor for acetyl-SCoA-carboxylase, an enzyme which convarts acetyl-CoA into malonyl-CoA. This step is thought to determine the rate at which fatty acids, such as palmitata ara synthesised in the sabaceous gland from precursors. This synthetic pathway can ba illustrated as follows:



Enzymes involved in fatty acid synthesis

1. Acetyl-SCoA carboxylase
2. Fatty acid synthetase
3. Deacylase

Palmitate and other fatty acids are the basic building blocks for triglycerides and provide some of

the precursors for wax and sterol esters. These lipid classes make up the bulk of human sebum. Therefore, it can be seen that inhibition of the enzyme acetyl-SCoA-carboxylase, which can be achieved by inhibiting biotin function using biotin antagonists, can significantly reduce the ability of sebaceous glands to synthesise lipids. This will, in turn, deplete the skin surface of lipids and reduce greasiness.

It is believed that at the molecular level, biotin functions to transfer and to help activate carbon dioxide derived from bicarbonate. The carbon dioxide must be transferred precisely from one enzymatic site to another; and be delivered in the correct orientetion and state of activetion by the biotin attached to the carrier protein as shown above. If this is not achieved, then the enzyme will not function. Hence it can be predicted that small perturbations in the biotin molecule, for example lengthening or shortening the biotin side chain, altering the cherge distribution of biotin or altering the shape of the biotin molecule, can render the acetyl-SCoA-carboxylase molecule inactive. Hence a very wide range of analogues of biotin, herein referred to as biotin antegonists, are biologically inactive with respect to the essential requirements of acetyl-SCoA-carboxylase. It can be deduced thet eny entegonist of biotin function of whatever nature can inhibit the activity of acetyl-SCoA-carboxylase.

Evidence of the effect of biotin antagonists on acetyl-SCoA-carboxylase activity

Experiments as described below were carried out using biotin sulphone as an example of a biotin antagonist.

1. In vitro experiments using cultured human fibroblasts

In preliminary experiments the ability of biotin sulphone to reduce the activity of acetyl-SCoA-carboxylase in an *in vitro* assey was accessed using cultured human dermal fibroblasts as described in Ghnelm et al (1981) Biochem. Soc. Trans. 9, 405—6 end references therein. Human dermal fibroblasts were maintained in culture for 3 days with 1 μm biotin sulphone in the presence of a nutrient medium containing 10% foetal calf serum. The level of naturally occurring biotin was about 10 nM. Enzyme activity was assayed in the cell pellet by the fixation of ^{14}C-sodium bicarbonate into protein in the presence of acetyl-CoA under appropriate conditions. Control experiments were done in the absence of biotin sulphone and enzyme activities were calculated with respect to protein.

The results obtained are shown in Teble 1 below:

Table 1

	nCi ^{14}C-bicarbonate fixed per mg protein	*Acetyl-SCoA-carboxylase activity (%)*
Control	4.46	100
Test (+1 μM biotin sulphone)	3.26	73

These results show that there was a 27% reduction in acetyl-SCoA-cerboxylase activity as a result of culture in the presence of biotin sulphone. A similar reduction was observed when the results were calculated in terms of nCi ^{14}C-bicarbonate incorporated into protein per mg of DNA.

2. In vivo experiments using rats

Experimental methodology

Ten, 3 week male weanling rets, clipped on left end right flanks, were divided into two groups of five animals. One group was untreated on the left flank while the right flank received the test solution (1 mg/ml biotin sulphone in 70% ethanol:30% water) twice a day (once per day at weekends) for six weeks. The second group received the ethanol/water carrier on the left flank and the test solution on the right. At the end of the treatment the rats were killed, skin removed end divided approximately into epidermis and dermis using a 0.2 mm keratatome cut. Samples of dermis contelning most of the sebaceous tissue from either untreated (UN), vehicle (V) or test (T) treated skin was incubated in a nutrient medium (basal eagles medium+ 10% foetal calf serum, 20 mM hepes pH 7.4, antibiotics, 100 μM sodium acetate) containing 1 μCi/ml sodium (1-^{14}C) acetate for 19 hours et 37°C. The ^{14}C-acetate is metabolically incorporated into lipids and gives a "snap shot" of the lipid synthesis profile over the 19 hour time period. At the end of the incubation samples were washed in ice cold medium without ^{14}C-acetate, quenched in ice cold 5% trichloroacetic acid (TCA), homogenised and centrifuged to separate insoluble residue from TCA soluble material ("TCA" fraction). The TCA fraction contains nucleotides, small metabolites especially succinate, amino acids, small peptides end free ^{14}C-acetate. Lipids were extracted in chloroform:methenol and subject to Folch washing essentially es described by Prottey et el, Brit. J. Dermatol. (1972) 87, 586—607 generating the following fractions: "lipids", "aqueous methanol" containing only a small proportion of skin lipids with a very low ^{14}C count and an extracted "solid residue". The totel ^{14}C count in all these fractions wes determined.

The radioactive lipids were fractionated into free fatty acids (FFA) monoglycerides (MG),

diglycerides (trace only) and triglycerides (TG) using a standerd, neutrel solvent, thin layer chrometography system.

Results

The following ratio provides a meesure of lipid synthesis per unit volume of skin, that is the total ^{14}C-acetate uptake into lipids (i.e. amount of lipid synthesis) divided by the 14C-acetete upteke into the remeining tissue fractions (i.e. e measure of sample size). (Remaining tissue="TCA" fraction+"solid residue").

The ratios derived in each of the ten rats are recorded in Table 2 below.

Table 2

	Treatment	
Rat	*CONTROL UN or V ratio*	*TEST test ratio*
A	0.74	0.43
B	0.94	0.23
C	0.37	0.59
D	0.65	0.44
E	0.58	0.52
F	0.25	0.53
G	0.55	0.58
H	0.63	0.39
I	0.75	0.73
J	0.53	0.43
	Av. 0.59	Av. 0.49—18%

Rats A—E received vehicle on their left flank
Rats F—J received no treetment on their left flenk

The deta show that topical epplication of biotin sulphone has caused an overell 18% reduction in ^{14}C-acetate uptake into dermel lipids. However ^{14}C-acetete is also incorporeted into the cholesterol synthetic pathway which should be largely uneffected by the biotin sulphone treatment. This will ceuse e "dilution" of the reduction seen ebove. Accordingly, the lipids whose synthesis is dependent on acetyl-SCoA-cerboxylase have been isolated. These are free fetty acids (FFA), monoglyceride (MG), diglycerlde (trece) and triglyceride (TG). It is predicted that e greeter reduction in the incorporetion of ^{14}C-ecetate into "triglyceride" lipid should now be observed. As fatty ecids are the primery product made by the acetyl-SCoA-carboxylase pathway in the sebeceous gland, results for this lipid class have been included sepereteły, as well as for totel "triglyceride" lipid; values for six of the rats are given in Table 3 below:

Table 3
Treatment

	FFA synthesis		*"Triglyceride" lipid*[b] *synthesis*	
Rat	*V+UN*	*Test*	*V+UN*	*Test*
A	1[a]	0.78	19.58	13.93
B	3.27	0.41	41.92	8.58
C	1.12	0.60	11.41	15.17
F	1.29	1.67	6.52	15.38
G	1.05	0.78	14.24	14.74
H	1.27	1.22	15.74	9.85
	Av. 1.50	Av. 0.91 —39%	Av. 18.24	Av. 12.94 —29%

Notes: (a) 1≡41,151 DPM ^{14}C-acetete incorporated into lipid including e correction for semple size, namely the ^{14}C-acetete upteke into the remaining tissue, as in Table 2.
(b) "Triglycerlde" lipid values are the sum of FFA+MG+TG.

The results show that biotin sulphone treatment reduces denovo FFA synthesis by 39% and "Triglyceride" (i.e. FFA+MG+TG) synthesis by 29% confirming the inhibitory action of biotin antagonists on acetyl-SCoA-carboxylase activity and on lipid synthesis in the sebaceous gland. The 29% reduction in FFA+MG+TG sebaceous lipid synthesis closely parallels the 27% drop in acetyl-SCoA carboxylase activity found for the *in vitro* cell culture assay system suggesting that the biotin sulphone treatment can be equally effective in reducing acetyl-SCoA-carboxylase activity in the cell culture system and in the rat sebaceous gland.

The invention is illustrated by the following examples:

Example 1

This Example illustrates a lotion according to the invention which is suitable for topical application to the skin of the face in order to reduce the secretion of sebum at the skin surface.

The lotion has the following formulation:

	% w/w
biotin sulphone	0.005
ethanol	99.995
perfume	q.s.

Example 2

This Example illustrates a hair tonic which is suitable for application to greasy hair or scalp for reducing the accumulation of sebum on the hair or scalp.

The hair tonic has the following formulation:

	% w/w
biotin sulphone	0.01
ethanol	50
water	49.99
perfume	q.s.

Example 3

This Example also illustrates a lotion which is suitable for topical application to the skin of the face in order to reduce the secretion of sebum at the skin surface.

The lotion has the following formulation:

	% w/w
homobiotin	0.015
propan-2-ol	10
ethanol	89.985
perfume	q.s.

Example 4

This Example also illustrates a hair tonic which is suitable for application to greasy hair or scalp for reducing the accumulation of sebum on the hair or scalp.

The hair tonic has the following formulation:

	% w/w
α-dehydrobiotin	0.02
ethanol	40
water	59.98
perfume	q.s.

Examples 5—8

The following formulations represent lotions which can be used topically in the treatment of greasy and/or acneic skin.

	% w/w			
	5	*6*	*7*	*8*
Hydroxyethyl cellulose	0.4	—	0.4	—
Absolute ethanol	25	25	25	25
Propane-1,2-diol	—	—	38.4	38.4
Butane-1,3-diol	38.4	38.8	—	—
Paramethyl benzoate	0.2	0.2	0.2	0.2
bisnordesthiobiotin	0.05	—	—	—
nordesthiobiotin	—	0.01	—	—
homobiotin	—	—	0.009	—
homobiotin methyl ester	—	—	—	0.15
Perfume	1	1	1	1
Water to	100	100	100	100

Examples 9—12

The following formulations represent lotions which can be used topically in the treatment of greasy and/or acneic skin.

	% w/w			
	9	*10*	*11*	*12*
Ethanol	10	10	10	10
Propane-1,2-diol	30	—	55	—
Butane-1,3-diol	—	30	—	55
bishomodesthiobiotin	0.1	—	—	—
trishomodesthiobiotin	—	0.2	—	—
desthiobiotin	—	—	—	0.15
perfume	q.s.	q.s.	q.s.	q.s.
Water to	100	100	100	100

Examples 13—16

The following formulations represent creams which can be used in the treatment of greasy skin.

	% w/w			
	13	*14*	*15*	*16*
Cetyl alcohol polyoxyethylene (10)	4	4	4	4
Cetyl alcohol	4	4	4	4
Mineral oil	4	2	—	—
Paraffin wax	—	2	4	—
Partial glyceride of palmitic and stearic acids	—	—	—	4
biotin sulphone	—	—	—	1
homobiotin sulphoxide	0.1	—	—	—
bishomobiotin sulphoxide	—	0.15	—	—
trishomobiotin sulphoxide	—	—	0.2	—
Triethanolamine	0.75	0.75	0.75	0.75
Butane-1,3-diol	3	3	3	3
Xanthan gum	0.3	0.3	0.3	0.3
Preservative	0.4	0.4	0.4	0.4
perfume	q.s.	q.s.	q.s.	q.s.
Water to	100	100	100	100

Example 17

The following formulation represents a lotion which can be used in the treatment of greasy and/or acneic skin.

	% w/w
Butane-1,3-diol	20
Ethanol	45
homobiotin sulphone	0.5
Perfume	q.s.
Water to	100

Example 18

This example illustrates a water-in-oil high internal phase emulsion containing bisnorbiotin sulphone according to the invention.

The emulsion consisted of 10% by volume oily phase and 90% by weight aqueous phase.

The oily phase and the aqueous phase had the following constitution:

	% w/w
Oily phase	
Sorbitan monooleate	20
Quarternium-18 hectorite	5
Liquid paraffin	75
Aqueous phase	
bisnorbiotin sulphone	0.5
Xanthan gum	1
Preservative	0.3
Perfume	q.s.
Sodium chloride (1% w/w solution)	to 100

The emulsion was prepared by taking 10 parts by volume of the oily phase and to it adding slowly with stirring 90 parts by volume of the aqueous phase.

The high internal phase water-in-oil emulsion so formed can be applied topically to improve skin condition generally or to alleviate greasiness and in the treatment of acne.

Example 19

This example illustrates a water-in-oil high internal phese emulsion containing homobiotin sulphone according to the invention.

The emulsion consisted of 10% by volume oily phase and 90% by weight aqueous phase.

The oily phase and the aqueous phase had the following constitution:

	% w/w
Oily phase	
Castor oil polyglyceryl ester	20
Hydrophobic silica	5
Sunflower seed oil	75
Aqueous phase	
homobiotin sulphone	0.8
Xanthen gum	1
Preservative	0.3
Perfume	q.s.
Sodium chloride (1% w/w solution)	97.9

The emulsion was prepared by taking 10 parts by volume of the oily phase and to it adding slowly with stirring 90 parts by volume of the aqueous phase.

The high internal phase water-in-oil emulsion so formed can be applied topically to improve skin condition generally or to alleviate greasiness and in the treatment of acne.

Examples 20 to 23

The following formulations represent lotions which can be used in the treatment of greasy and/or acneic skin.

	% w/w			
	20	*21*	*22*	*23*
Hydroxyethyl cellulose	0.4	—	0.4	—
Absolute ethanol	20	15	21	21
Propane-1,2-diol	—	—	38.4	38.4
Butane-1,3-diol	38.4	38.8	—	—
Pare methyl benzoate	0.2	0.2	0.2	0.2
homobiotin sulphone	0.2	—	—	—
bishomobiotin sulphone	—	2	—	—
trishomobiotin sulphone	—	—	5	—
bisnorbiotin sulphone	—	—	—	1
Perfume	1	1	1	1
Water	to 100	100	100	100

Examples 24 to 27

The following formulations represent lotions which can be used in the treatment of greasy and/or acneic skin.

	% w/w			
	24	*25*	*26*	*27*
Ethanol	10	10	8	5
Propane-1,2-diol	30	0	55	0
Butane-1,3-diol	0	30	0	55
Ethyl lactate	6	9	11	14
norbiotin methyl ester	0.8	—	—	—
homobiotin methyl ester	—	1.2	—	—
bishomobiotin methyl ester	—	—	1.5	—
trishomobiotin methyl ester	—	—	—	0.7
perfume	q.s.	q.s.	q.s.	q.s.
water	to 100	100	100	100

The following examples 28 to 32 illustrate shampoos for use in the treatment of greasy hair and scalp.

Example 28

	% w/w
Sodium lauryl ether sulphate (2 EO): 21% AD	41.1
Lauryl dimethylamino acetic acid bentaine: 30% AD	4
Coconut fatty acid diethanolamide	1.5
Oleyl triethoxy phosphate (BRIPHOS 03D)	1
Polyglycol-polyamine condensation resin (POLYQUART H): 50% active	1.5
Preservative, colouring matter, salt	0.58
Oxybiotin sulphonic acid	5
Perfume	q.s.
Water	to 00

Example 29

	% w/w
Sodium lauryl ether sulphate (2 EO): 100% AD	12
POLYQUART H: 50% active	2.5
BRIPHOS 03D	2.5
γ-(2,3-ureylenecyclohexyl)butyric acid	4
Perfume	q.s.
Water	to 100

Example 30

	% w/w
Monoethanolamine lauryl sulphate: 100% AD	20
POLYQUART H: 50% active	3
BRIPHOS 03D	1.7
Coconut diethanolamide	5
Biotin sulphone	1
Perfume	q.s.
Water	to 100
pH adjusted to 6.5.	

Example 31

	% w/w
Sodium lauryl ether sulphate (3 EO): 100% AD	12
POLYQUART H: 50% active	0.3
BRIPHOS 03D	1
γ-(3,4-ureylenecyclohexyl)valeric acid	2
Perfume	q.s.
Water	to 100
pH adjusted to 6.5.	

Example 32

	% w/w
Sodium lauryl ether sulphate (2 EO): 100% AD	12
POLYQUART H: 50% active	3
BRIPHOS 03D	1
Opacifier	9
2-oxo-4-imidazolidine caproic acid	5
Perfume	q.s.
Water	to 100
pH adjusted to 6.5.	

Examples 33—36

The following formulations represent lotions which can be used in the treatment of greasy and/or acneic skin.

	% w/w			
	33	*34*	*35*	*36*
Hydroxyethyl cellulose	0.4	—	0.4	—
Absolute ethanol	25	25	25	25
Propane-1,3-diol	—	—	38.4	38.4
Butane-1,3-diol	38.4	38.8	—	—
Para methyl benzoate	0.2	0.2	0.2	0.2
Thiazolidine	5	—	—	—
Methyl-1,3-acetyl-4-thiazolidine carboxylate	—	0.3	—	—
1,3-propyl-2-acetyl-4-thiazolidine carboxylate	—	—	0.8	—
2-piperidone-6-carboxylic acid hydrazide	—	—	—	1.2
Perfume	1	1	1	1
Water	to 100	100	100	100

Examples 37—41

The following formulations represent lotions which can be used in the treatment of greasy and/or acneic skin.

	% w/w				
	37	*38*	*39*	*40*	*41*
Ethanol	10	10	10	10	10
Propane-1,2-diol	30	—	55	—	30
Butane-1,3-diol	—	30	—	55	—
γ-(2-carboxy-3-indolyl)butyric acid hydrazide	0.004	—	—	—	—
2-imidazoline-4-caproic acid hydrazide	—	0.008	—	—	—
2-imidazoline-4-valeric acid hydrazide	—	—	0.04	—	—
Biotin sulphone	—	—	—	0.9	—
Biotin hydrazide	—	—	—	—	0.1
Perfume	q.s.	q.s.	q.s.	q.s.	q.s.
Water	to 100	100	100	100	100

Examples 42—47

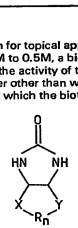
The following Examples 42 to 47 illustrate powder compositions according to the invention which can be applied topically to moist, greasy skin.

	% w/w					
	42	*43*	*44*	*45*	*46*	*47*
Chemically modified starch	5	—	5	—	5	—
Chemically modified cellulose	—	5	—	5	—	5
Boric acid	10	10	10	10	10	10
Zinc oxide	5	5	5	5	5	5
Biotin sulphone	5	—	—	—	—	—
Biotin sulphone methyl ester	—	10	—	—	—	—
Homobiotin sulphone	—	—	2	—	—	—
Homobiotin sulphone methyl ester	—	—	—	4	—	—
Bishomobiotin sulphone	—	—	—	—	1	—
Bishomobiotin sulphone methyl ester	—	—	—	—	—	3
Perfume	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Chalk	10	10	10	10	10	10
Talc	to 100	100	100	100	100	100

Claims

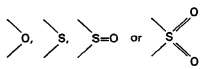
1. A cosmetically acceptable composition for topical application to human skin or hair which comprises, at a concentration of from 0.0001M to 0.5M, a biotin antagonist, or a salt thereof, or mixtures thereof, which is capable of blocking the activity of the biotin-dependent enzyme acetyl-SCoA-carboxylase; together with a liquid carrier other than water.

2. A composition according to claim 1, in which the biotin antimetabolite has the structure (I):



(I)

where n is zero or 1
and when
n is zero,
X is $-CH_2-$, and
Y is $-(CH_2)_mZ$
and when
n is 1,

R is chosen from  or

X is  , and Y is 

where
m is an integer of from 1 to 8, and
Z is chosen from $-CH_2COOH$, $-CH{=}CHCOOH$, $-CH(CH_3)COOH$, $-CH_2COOCH_3$, $-NHNH_2$ and $-SO_3H$

provided that when n is 1, R is  ,

and Z is $-CH_2COOH$, then m is an integer of from 1 to 3, or 5 to 8.

3. A composition according to claim 2, in which, in the structure of the biotin antagonist,
n is zero, and
Z is $-CH_2COOH$

4. Composition according to claim 3, in which the biotin antagonist is chosen from trisnordesthiobiotin, bisnordesthiobiotin, nordesthiobiotin, desthiobiotin, homodesthiobiotin, bishomodesthiobiotin, trishomodesthiobiotin, tetrahomodesthiobiotin, and mixtures thereof.

5. A composition according to claim 2, in which, in the structure of the biotin antagonist,
n iz zero, and
Z is $-CH(CH_3)COOH$

6. A composition according to claim 5, in which the biotin antagonist is α-methyldesthiobiotin.

7. A composition according to claim 2, in which, in the structure of the biotin antagonist,
n is 1,

R is  ,

and
Z is $-CH_2COOH$

8. A composition according to claim 7, in which the biotin antagonist is chosen from trisnorbiotin sulphoxide, bisnorbiotin sulphoxide, norbiotin sulphoxide, biotin sulphoxide, homobiotin sulphoxide, bishomobiotin sulphoxide, trishomobiotin sulphoxide and mixtures thereof.

9. A composition according to claim 2, in which, in the structure of the biotin antagonist,
n is 1,

and

Z is —CH_2COOH

10. A composition according to claim 9, in which the biotin antagonist is chosen from trisnorbiotin sulphone, bisnorbiotin sulphone, norbiotin sulphone, biotin sulphone, homobiotin sulphone, bishomobiotin sulphone, trishomobiotin sulphone and mixtures thereof.

11. A composition according to claim 2, in which, in the structure of the biotin antagonist, n is 1,

Z is —CH_2COOH or —CH_2COOCH_3, and
m is an integer of from 1 to 3 or 5 to 8.

12. A composition according to claim 11, in which the biotin antagonist is chosen from trisnorbiotin, bisnorbiotin, norbiotin, homobiotin, bishomobiotin, trischomobiotin, and mixtures thereof.

13. A composition according to claim 2, in which, in the structure of the biotin antagonist, n is 1

and

Z is —CH=CHCOOH or —$CH_2(CH_3)COOH$.

14. A composition according to claim 13, in which the biotin antagonist is chosen from α-dehydrobiotin, α-methylbiotin and a mixture thereof.

15. A composition according to claim 2, in which, in the structure of the biotin antagonist, n is 1,

and

Z is —CH_2COOH.

16. A composition according to claim 15, in which the biotin antagonist is chosen from trisnoroxybiotin, bisnoroxybiotin, noroxybiotin, oxybiotin, homooxybiotin, bishomooxybiotin, trishomooxybiotin, and mixtures thereof.

17. A composition according to claim 2, in which, in the structure of the biotin antagonist, n is 1

and

Z is —SO_3H.

18. A composition according to claim 17, in which the biotin antagonist is chosen from trisnoroxybiotin sulphonic acid, bisnoroxybiotin sulphonic acid, noroxybiotin sulphonic acid, oxybiotin sulphonic acid, homooxybiotin sulphonic acid, bishomooxybiotin sulphonic acid, trishomooxybiotin sulphonic acid, and mixtures thereof.

19. A composition according to claim 2, in which, in the structure of the biotin antagonist, n is 1,

and

Z is —CH_2COOCH_3.

20. A composition according to claim 19, in which the biotin antagonist is chosen from trisnorbiotin methyl ester, bisnorbiotin methyl ester, norbiotin methyl ester, homobiotin methyl estar, bishomobiotin methyl ester, trishomobiotin methyl ester, tetrahomobiotin methyl ester, and mixtures thereof.

21. A composition according to claim 2, in which, in the structure of the biotin antagonist, n is 1,

and

Z is $-CH_2COOCH_3$.

22. A composition according to claim 21, in which the biotin antagonist is chosen from trisnorbiotin sulphone methyl ester, bisnorbiotin sulphone methyl ester, norbiotin sulphone methyl ester, biotin sulphone methyl ester, homobiotin sulphone methyl ester, bishomobiotin sulphone methyl ester, trishomobiotin sulphone methyl ester, tetrahomobiotin sulphone methyl aster, and mixtures thereof.

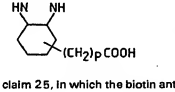
23. A composition according to claim 2, in which, in the structure of the biotin antagonist, n is 1,

and

Z is $-NHNH_2$.

24. a composition according to claim 23, in which the biotin antagonist is chosen from trisnorbiotin hydrazide, bisnorbiotin hydrazide, norbiotin hydrazide, biotin hydrazide, homobiotin hydrazida, bishomobiotin hydrazida, trishomibiotin hydrazide, and mixtures thereof.

25. A composition according to claim 1, in which the biotin antagonist has the structure:



(II)

where p is 2 to 5.

26. A composition according to claim 25, in which the biotin antagonist having the structure (II) is chosen from:

γ-(2,3-ureylenecyclohexyl)butyric acid,
δ-(2,3-ureylenecyclohexyl)valeric acid,
γ-(3,4-ureylenecyclohexyl)butyric acid,
δ-(3,4-ureylenecyclohexyl)veleric acid, and mixtures thereof.

27. A composition according to claim 1, in which the biotin antagonist is chosen from:

2-oxo-4-imidazolidine caproic acid, thiezolidine,
methyl-1,3-acetyl-4-thiazolidine carboxylate, 1,2-propyl-2-acetyl-4-thiezolidine carboxylate methyl ester, and its hydrazide,
2-piperidone-6-carboxylic acid hydrezide,
γ-(2-carboxy-3-indolyl)butyric acid hydrazide,
2-imidazoline-4-carboxylic acid hydrazide,
2-imidazoline-4-caproic acid hydrazida,
2-imidazoline-4-valeric acid hydrazide,
ureylenatetrahydrofuryl aliphatic sulphonic acids, benzyl thio esters,
semicarbazides of biotin,
bishydrazides of suberic ecid end sebecic ecids, and mixtures thereof.

28. A composition according to any preceding claim, in which the concentretion of the biotin antimetabolite is from 0.001 M to 0.1 M.

29. A composition according to any preceding claim, in which the concentration of the biotin antimetabolite is from 0.01M to 0.1M.

30. A composition according to any of claims 1 to 29, in which the biotin antimetabolite forms from 0.004 to 10% by weight of the composition.

31. A composition according to any of claims 1 to 29, in which the biotin antimetabolite forms from 0.03 to 2% by weight of the composition.

32. A composition according to any of claims 1 to 29, in which the biotin antimetabolite forms from 0.2 to 2% by weight of the composition.

33. A composition according to any preceding claim, in which the carrier other than water is a C_1 to C_6 alkanol and mixtures thereof.

34. The composition according to claim 33, in which the alkanol is chosen from ethanol, propane-1-ol, propane-2-ol and mixtures thereof.

35. A composition according to any of claims 1 to 32, in which the carrier is a powder.

36. A composition according to any preceding claim, in which the carrier other than water forms from 50 to 99.996% by weight of the composition.

37. A composition according to any preceding claim, in which the carrier other than water forms from 90 to 99.5% by weight of the composition.

38. A composition according to any preceding claim, which further comprises water.

39. A process for preparing a composition according to any preceding claim, which comprises the step of mixing a biotin antagonist with a suitable carrier other than water, the concentration of the biotin antagonist being from 0.0001M to 0.5M.

40. A method of treating the human skin or hair to reduce greasiness, which comprises the step of contacting the skin or hair with an effective amount of the composition according to any of claims 1 to 38.

41. The use of biotin antagonists and compositions containing them according to any of claims 1 to 38 in the treatment of greasy human skin or hair.

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